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One-Pot Procedure for the Synthesis of *N*-Fumaroyl-2-Oxazolidinones

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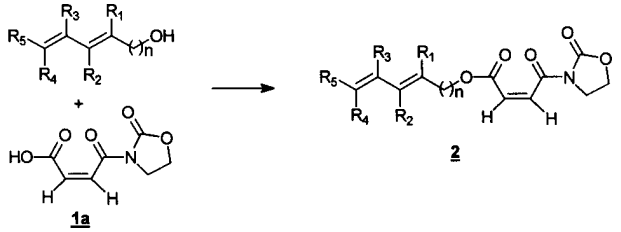
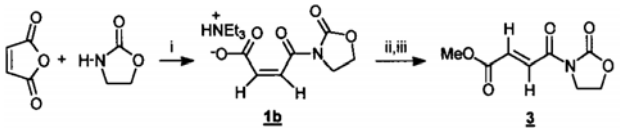
Abstract: Reaction of maleic anhydride with 2-oxazolidinone in the presence of triethylamine yields mono functionalized maleic acid, which is transformed into functionalized *N*-fumaroyl-2-oxazolidinones in 45-56% overall yields by treatment with oxalyl chloride and subsequent reaction with nucleophiles.

The intramolecular Diels Alder (IMDA) reaction is probably one of the most convenient methodologies for the construction of a wide variety of annulated carbon frameworks.[1] With respect to asymmetric synthesis the possible control over several newly formed stereogenic centers in this process is challenging. Although recently catalytic enantioselective versions have been reported making use of chiral Lewis acids,[2] most studies with these type of catalysts have focussed on intermolecular Diels Alder reactions. Our interests included the possible synthesis of suitable substrates for IMDA reactions with chiral Lewis acids. This strategy includes the presence of an *N*-acyl-2-oxazolidinone derivative from a maleic acid residue as the dienophilic part of the substrate. We envisaged that such a synthesis would require a formal coupling of the resulting acid **1a** with a suitable dienol via esterification as the key step to yield the required triene system **2** (scheme 1)[3].



Scheme 1

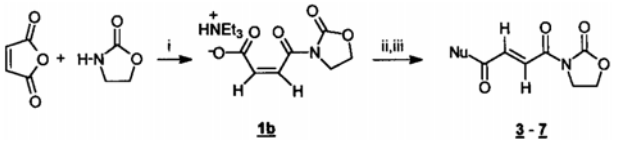
The synthesis of the dienophilic part was easily accomplished by reaction of maleic anhydride with 2-oxazolidinone in the presence of triethylamine as a base. This reaction, monitored by ^{1}H NMR, showed clean conversion with stoichiometric amounts of anhydride and 2-oxazolidinone after 16 h at room temperature (> 90% yield). The triethylammonium salt **1b** was used without further workup, since attempted isolation of the free carboxylic acid was plagued by water solubility.[4] At this stage we anticipated that for the final introduction of a dienol an overall one-pot procedure would be the most logical and economic choice. So, treatment of **1b** with oxalyl chloride, followed by reaction with methanol in the presence of pyridine afforded a white solid in 45% overall yield after chromatographic purification. ^{1}H NMR analysis, however, showed a large coupling constant for the olefinic protons (^3J = 15.6 Hz) indicative for the fact that the fumarate **3** instead of the maleate had been obtained (scheme 2).[5]



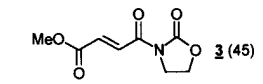
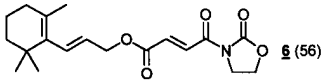
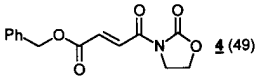
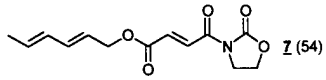
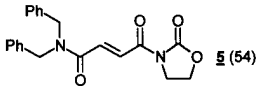
Scheme 2. i) NEt_3, CH_2Cl_2, RT 16 h. ii) $(COCl)_2$, DMF (cat), RT 3 h. iii) MeOH, pyr., RT 1h.

This result was not completely unexpected, since the acid catalyzed isomerization of maleates to fumarates is a well known process.[6] The new process proved to applicable to several other nucleophiles as can be seen from the results summarized in the table.[7] Non-symmetric fumarates such as benzyl ester **4**[8] and dibenzylamide **5**[9] were easily obtained by this methodology in 49 and 53% isolated yields, respectively. The coupling of dienols was also readily accomplished, resulting in the synthesis of substrates **6**[10] and **7**[11] for chiral Lewis acid catalyzed IMDA reactions in, respectively, 56 and 54% overall yield.

Table. Synthesis of *N*-fumaroyl-2-oxazolidinones



Reagents and conditions: i) NEt_3, CH_2Cl_2, RT 16 h. ii) $(COCl)_2$, DMF (cat), RT 3 h. iii) NuH, pyr., RT 1h.

N-fumaroyl-2-oxazolidinone (yield (%))[a]	
 **3** (45)	 **6** (56)
 **4** (49)	 **7** (54)
 **5** (54)	

a) Isolated yields

This synthetic methodology might well be applied for the introduction of other functionalized side chains which would yield potent substrates for other types of catalytic enantioselective transformations.

In summary we have demonstrated a simple and straightforward one-pot procedure for the synthesis of *N*-fumaroyl-2-oxazolidinones. Catalytic asymmetric studies applying these substrates are in progress.

Acknowledgement
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References and Notes

1. (a) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (b) Feringa, B.L.; Gelling, O.J.; Meesters, L. *Tetrahedron Lett.* **1990**, *31*, 7201.
2. (a) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231. (b) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947. (c) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymm.* **1991**, *2*, 1305.
3. For related strategies, see: (a) Grieco, P.A.; Nargund, P. *Tetrahedron Lett.* **1986**, *27*, 4813. (b) He, J.-F.; Wu, Y.-L. *Tetrahedron* **1988**, *44*, 1933.
4. Triethylammonium salt **1b**, was prepared by reaction of 2-oxazolidinone (11 mmol) and maleic anhydride (11 mmol) in dry dichloromethane (20 ml) in the presence of triethylamine (12 mmol) at room temperature for 16 h. This solution was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.3 Hz, 9H), 3.08 (q, *J* = 7.3 Hz, 6H), 4.02 (t, *J* = 8 Hz, 2H), 4.39 (t, *J* = 8 Hz, 2H), 6.39 (d, *J* = 12 Hz, 1H), 6.76 (d, *J* = 12 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 8.33, 41.94, 44.73, 61.71, 119.47, 140.00, 152.98, 164.97, 171.67.
5. This compound was identical to the material obtained by other reported methods, see: (a) Knol, J.; Feringa, B.L. accepted for publication. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, *J. Am. Chem. Soc.* **1989**, *111*, 5340.
6. (a) Small amounts (< 10%) of the maleate, which could be detected in the ^{1}H NMR spectrum of the crude product, were efficiently removed by chromatography. (b) Campbell, P.G.; Sumrell, G.; Schramm, C.H. *J. Org. Chem.* **1961**, *26*, 697.
7. All *N*-fumaroyl-2-oxazolidinones were prepared according to the following typical procedure using inert conditions: To a cooled solution (0 °C) of the triethylammonium salt **1b** in dry dichloromethane (20 ml), containing five drops of dry DMF, was added oxalyl chloride (11 mmol) and the mixture was stirred for 3 h at room temperature. After recooling (0 °C) a pyridine solution (5 ml) of the nucleophile (1.2 - 3 eq.) was added and the dark brown mixture was stirred for 1 h at room temperature followed by filtration over silica gel (~ 50 g) with a ethyl acetate/petroleum ether (40-60) mixture. Further purification by column chromatography over silica gel afforded the pure product.
8. White solid: mp 81.2-83.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.09 (t, *J* = 7.9 Hz, 2H), 4.48 (t, *J* = 7.9 Hz, 2H), 5.26 (s, 2H), 7.00 (d, *J* = 15.4 Hz, 1H), 7.38 (m, 5H), 8.20 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 42.34 (t), 62.20 (t), 66.83 (t), 128.08 (d), 128.24 (d), 128.40 (d), 132.17 (d), 133.59 (d), 135.08 (s), 152.91 (s), 163.43 (s), 164.43 (s); Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found C, 61.23; H, 4.76; N, 5.17.
9. White solid: mp 143.4-144.7 C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.06 (t, *J* = 7.9 Hz, 2H), 4.45 (t, *J* = 7.9 Hz, 2H), 4.52 (s, 2H), 4.64 (s, 2H), 7.28 (m, 10H), 7.54 (d, *J* =15.4 Hz, 1H), 8.20 (d, *J* =15.4 Hz, 1H) ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 42.16 (t), 47.97 (t), 49.78 (t), 61.96 (t), 126.29 (d), 127.21 (d), 127.46 (d), 128.00 (d), 128.25 (d), 128.57 (d), 129.84 (d), 134.28 (d), 135.52 (s), 136.19 (s), 152.72 (s), 163.73 (s), 164.94 (s); Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found C, 69.27; H, 5.63; N, 7.69.
10. (a) Glassy colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.43 (m, 2H), 1.57 (m, 2H), 1.66 (s, 3H), 1.95 (m, 2H), 4.09 (t, *J* = 8.1 Hz, 2H), 4.47 (t, *J* = 8.1 Hz, 2H), 4.74 (dd, *J* = 6.4, 1.3 Hz, 2H), 5.54 (dt, *J* = 15.8, 6.41 Hz, 1H), 6.21 (d br, *J* = 15.8 Hz, 1H), 6.96 (d, *J* = 15.8 Hz, 1H), 8.15 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.99 (t), 21.18 (q), 32.53 (t), 33.68 (s), 39.19 (t), 42.43 (t), 62.21 (t), 66.32 (t), 126.11 (d), 129.68 (s), 131.74 (d), 133.59 (d), 134.08 (d), 136.17 (s), 152.90 (s), 163.64 (s), 164.46 (s); HRMS Calcd for $C_{19}H_{25}NO_5$: 347.173. Found: 347.173.
(b) For a related catalytic enantioselective *intermolecular* Diels Alder reaction see: Knol, J.; Feringa, B.L. *Tetrahedron: Asymm.* **1995**, *6*, 1069.
11. White solid: mp 72.5-75.0 C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.77 (d, *J* = 6.8 Hz, 3H), 4.10 (t, *J* = 8.6 Hz, 2H), 4.48 (t, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 6.4 Hz, 2H), 5.72 (m, 2H), 6.06 (m, 1H), 6.30 (dd, *J* = 15, 10.3 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 8.16 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.01 (q), 42.45 (t), 62.25 (t), 65.68 (t), 122.73 (d), 130.13 (d), 131.59 (d), 131.84 (d), 133.97 (d), 135.36 (d), 152.95 (s), 163.61 (s), 164.43 (s); HRMS Calcd for $C_{13}H_{15}NO_5$: 265.095. Found: 265.095.